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Breast Cancer and Oral Contraceptive Use in Asian-American Women

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Breast cancer incidence has historically been 4–7 times higher in the United States than in Asia. A previous study by the authors in Asian-American women demonstrated a substantial increase in breast cancer risk in women who migrated from Asia to the United States, with the risk almost doubling during the first decade after migration. Increased use of oral contraceptives soon after migration to the United States could possibly explain this rapid rise in risk. In a population-based case-control study of Chinese, Filipino, and Japanese-American women, aged 20–55 years, who lived in San Francisco-Oakland, California; Los Angeles, California; and Oahu, Hawaii during 1983–1987, 597 cases (70% of those eligible) and 966 controls (75%) were interviewed. Controls were matched to cases on age, ethnicity, and area of residence. Oral contraceptive (OC) use increased with time since migration; 15.0% of Asian-born women who had been in the West <8 years, 33.4% of Asian-born women who had been in the West ≥8 years, and 49.6% of Asian women born in the West had ever used OCs. However, duration of OC use (adjusted for age, ethnicity, study area, years since migration, education, family history of breast cancer and age at first full-term birth) was not associated with increased risk of breast cancer. Moreover, neither OC use before age 25 years nor before first full-term birth was associated with increased risk. Results were unchanged when restricted to women under age 45 years or under age 40 years. After adjustment for duration of OC use, women who had been in the United States ≥8 years were still at almost twice the risk of breast cancer compared with women who had been in the United States 2–7 years. This study suggests that OC use cannot explain the elevated risk observed in Asian women who migrated to the United States ≥7 years ago. *Am J Epidemiol* 1999;150:561–7.

Asian Americans; breast neoplasms; contraceptives, oral; transients and migrants

Breast cancer incidence rates have historically been 4–7 times higher in the United States than in China or Japan (1). Although the rates in Asia have increased substantially over the past decades, there is still a large discrepancy in breast cancer rates between countries (2). A number of early migrant studies showed that when Asian women move to the United States, their breast cancer rates increased over several generations, but increased only slightly in the migrating generation (see reference 3 for a review). However, a study by Kolonel et al. (4), as well as our population-based case-control study of women of Chinese, Filipino, and Japanese ethnicities who lived in the United States (3), demonstrated a substantial increase in breast cancer rates in the migrating generation.

Such a rapid increase in risk may be due to changes in modifiable life-style factors. Oral contraceptive (OC) use represents one such life-style factor. While early studies were largely reassuring of no increased risk with OC use (5–11), a number of more recent studies have found an association between long-term use of OCs and breast cancer in young women (12–22). A recently published report from the Collaborative Group on Hormonal Factors in Breast Cancer (23, 24) found an increased risk associated with recent OC use; the effect was strongest in the subgroup that started use at an early age. Because OC use has been much lower in Asian countries than in the United States (25, 26), we hypothesized that part of the rapid increase in breast cancer risk that occurs among these relatively young Asian women who migrate to the United States could be due to OC use.

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Abbreviations: CI, confidence interval; OC, oral contraceptive; OR, odds ratio.

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MATERIALS AND METHODS

The methods of this study have been previously described (3). Briefly, eligible cases were all women of Chinese, Japanese, or Filipino ethnicity who were diagnosed with histologically confirmed, first primary breast cancer at ages 20–55 years in the San Francisco-Oakland Metropolitan Statistical Area (MSA), the Los Angeles MSA, or Oahu, Hawaii, during the period April 1, 1983 through June 30, 1987. Controls were frequency matched to the expected case distribution on study area, ethnicity, and year of birth (5-year groups), using a 2:1 ratio whenever possible. In the San Francisco-Oakland and Los Angeles study areas, potential control subjects were selected with random-digit dialing, while in Hawaii they were selected with the Health Surveillance Program of the Hawaii Department of Health, which annually samples 2 percent of the households in the state. To be eligible for the study, a case or control had to be at least 50 percent Chinese, Japanese, or Filipino, or a 50 percent mixture of these ethnicities. In addition the case or control had to be living in the San Francisco-Oakland MSA, the Los Angeles MSA, or Oahu at the time of interview. Control subjects with previous breast cancer or with double mastectomies were excluded.

Households selected by random-digit dialing as potential sources of control subjects were screened to determine the ethnicity and age range of all females who received telephone calls at that number. Using random-digit dialing, a total of 18,680 households were contacted in Los Angeles and 15,265 households in San Francisco-Oakland. The response rate for the screening interview was 92 percent in Los Angeles and 91 percent in San Francisco-Oakland. Non-responding households either could not be contacted after successive calls or refused to complete the household census.

Of 852 eligible cases, 597 (70 percent) participated; of the 1,287 eligible controls identified, 966 (75 percent) participated. Taking into account the response rate on the screening interview, the overall response rate among controls was 71 percent. Major reasons for not participating were subject refusal (19 percent among cases and 23 percent among controls), death (6 percent among cases), and physician refusal (4 percent among cases). The participation rates were similar in the three study areas both for cases (68–75 percent) and for controls (70–79 percent). Each study area contributed approximately one-third of the subjects.

Cases and controls were interviewed in their homes by trained interviewers with standardized questionnaires. The subject selected the language of the interview: English, Japanese, or Chinese.

In order to assess exposures among control subjects only up to a time similar to that of cases, a reference age comparable to the age at diagnosis of breast cancer for the case patients was assigned to each of the control subjects in the following manner. Cases and controls were stratified for ethnicity, study area, year of birth (5-year groups), and age at interview (above or below the median of the case patients) in each stratum. The mean difference between date of diagnosis and date of interview for the case patients in each stratum was subtracted from the age at interview for each control subject in the stratum to generate an assigned reference age (3). However, because proportionally more cases than controls were interviewed within 3 years after diagnosis/reference age and because the questions on OCs obtained information on OCs used up until 3 years prior to the interview date, we excluded OC use that fell within 3 years of the diagnosis/reference date.

We used the same categorization of countries ("East," "West," and "other"), as was previously used by Ziegler et al. (3) when describing the association between migration patterns and breast cancer risk in this study (3). "East" included China, Taiwan, Hong Kong, Macao, Japan, the Philippines, Southeast Asia, the Malaysian Peninsula, Singapore, India, and countries in the southwest Pacific Ocean except Australia and New Zealand. "West" included the United States, with Guam, Midway Island, and its other Pacific Territories, Canada, western Europe, central Europe, the USSR, Australia, and New Zealand. All other countries were categorized as "other."

We calculated odds ratios and 95 percent confidence intervals as estimates of relative risk using unconditional logistic regression, while adjusting for potential confounders in the model (27). We adjusted all odds ratios for age at diagnosis (5-year categories); study area (San Francisco-Oakland, Los Angeles, Oahu); ethnicity (Chinese, Japanese, Filipino); years since migration (born in the West, ≤1 year in West, 2–7 years in West, ≥8 years in West, ≥1 East-West move); education category (high school, some college, college); family history of breast cancer (first degree, second degree, none); and age at first full-term birth (≤19, 20–24, 25–29, >29 years, none).

To determine whether variables such as ethnicity, study location, years since migration, and age at diagnosis were effect modifiers, we tested whether the fit of the baseline multivariate logistic regression model with a single OC duration variable was improved by fitting separate OC duration categories for each subgroup. The p value for this likelihood ratio (LR) test is provided in the tables.

For these analyses, we excluded 23 subjects (16 controls and 7 cases) with missing information on OC use, and 5 controls with a reference age prior to age at

migration. We present the results for 590 cases and 945 controls.

RESULTS

Selected demographic characteristics among cases and controls are displayed in table 1. In previous publications from this study, years since migration (3), height, recent weight, and weight change (28) were all found to be associated with risk; age at first live birth and number of live births were inversely associated, while age at menarche (29) and tofu intake (30) were only slightly associated with breast cancer risk.

TABLE 1. Demographic characteristics of 590 cases and 945 controls in a case-control study of Asian-American women and oral contraceptive use, 1983–1987

	Cases		Controls	
	No.	%	No.	%
Age at diagnosis (years)*				
<30	9	1.5	27	2.9
30–39	127	21.5	240	25.4
40–49	259	43.9	373	39.5
≥50	195	33.1	305	32.3
Ethnicity				
Chinese	163	27.6	282	29.8
Japanese	238	40.3	386	40.8
Filipino	189	32.0	277	29.3
Study location				
Hawaii	211	35.8	370	39.2
Los Angeles	214	36.3	272	28.8
San Francisco	165	28.0	303	32.1
Years since migration				
US born	252	42.7	355	37.6
≤1 year in West	18	3.1	35	3.7
2–7 years in West	51	8.6	140	14.8
≥8 years in West	219	37.1	329	34.8
≥1 East-West move	50	8.5	86	9.1

* A comparable "age at diagnosis" or reference age was assigned to controls (see text).

The prevalence of OC use for controls by time since migration from the East to the West is shown in table 2. Women who had been in the West for 2–7 years had the lowest prevalence of use; 15.0 percent had used OCs, and only 1.4 percent had used OCs for ≥5 years. Asian Americans born in the West had the highest prevalence of OC use: 49.6 percent had used OCs, and 14.6 percent had used OCs for ≥5 years. There was little difference in frequency of OC use between women who had lived in rural or urban areas while in the East.

There was no increased risk associated with ever use of OCs or with duration of OC use (table 3). If anything, there was a suggestion of a decreasing risk of breast cancer with increasing duration of use beyond one year. Compared with never users, women who started using OCs at an early age were not at an increased risk of breast cancer, and were possibly at decreased risk with very early onset of use (age ≤21 years). Use before first full-term birth was also not associated with increased risk of breast cancer.

Because it has been suggested that the effect of OC use is primarily an effect of recent use, we examined the effect of time since last use. Compared with never use, recent use (time since last OC use <5 years prior to diagnosis) was not associated with an increased risk of breast cancer. There was also no suggestion of decreasing risk with increasing time since last use. In all these analyses, the unadjusted and adjusted models were very similar.

We also examined whether there could be effect modification by certain demographic variables such as ethnicity, residence (study location), years since migration, and age at diagnosis (table 4). There was no apparent effect modification by ethnicity, study location, or age at diagnosis. There was an apparent inverse associ-

TABLE 2. Frequency of oral contraceptive (OC) use among Asian-American controls by time since migration to the West and urban/rural residence in the East, 1983–1987

Years since migration	Urban or rural residence in East	Total no. of controls*	Women who had used OCs			
			Ever		>60 months	
			No.	%	No.	%
2–7	All	140	21	15.0	2	1.4
	Always rural	36	6	16.7	1	2.8
	Always urban	89	13	14.6	1	1.1
	Rural/urban moves†	15	2	13.3	0	0.0
≥8	All	329	110	33.4	24	7.3
	Always rural	79	24	30.4	5	6.3
	Always urban	220	75	34.1	15	6.8
	Rural/urban moves†	30	11	36.7	4	13.3
Born in West		355	176	49.6	52	14.6

* Excluding 35 controls who migrated ≤1 year prior to assigned reference age and 86 controls with ≥1 East-West move.

† Includes women with ≥1 rural to urban move.

TABLE 3. Odds ratio (ORs) of breast cancer associated with ever use and pattern of use of oral contraceptives (OCs) in Asian-American women, 1983–1987

Risk factor	Level	No. of cases	No. of controls	Unadjusted OR	Adjusted OR*	95% CI*
Ever use of OCs	Never	383	594	1.00	1.00	
	Ever	207	351	0.92	0.91	0.72, 1.15
Duration of OC use (in months)	Never used OCs	383	594	1.00	1.00	
	1–12	83	111	1.16	1.20	0.86, 1.69
	13–60	79	153	0.80	0.81	0.58, 1.12
	>60	45	87	0.80	0.71	0.47, 1.07
					$p = 0.03$†	
Age at start of OC use (in years)	Never used OCs	383	594	1.00	1.00	
	>35	19	23	1.28	1.23	0.62, 2.44
	30–35	56	84	1.03	0.87	0.59, 1.28
	25–29	74	101	1.14	1.10	0.77, 1.58
	22–24	42	91	0.72	0.86	0.56, 1.32
	≤21	16	52	0.48	0.46	0.24, 0.87
					$p = 0.16$‡	
OC use before first full-term birth (FFTB)§	Never used OCs	383	594	1.00	1.00	
	Used OCs before FFTB	59	121	0.76	0.80	0.54, 1.19
	No (after FFTB only)	99	196	0.78	0.87	0.64, 1.17
	No FFTB, used OCs	18	8	3.49	2.23	0.88, 5.66
OC use before age 25 years	Never used OCs	383	594	1.00	1.00	
	Used OCs before age 25	58	143	0.63	0.70	0.48, 1.03
	No (after age 25 years only)	149	208	1.11	1.01	0.77, 1.32
Time since stopped OC use (in years)¶	Never used OCs	383	594	1.00	1.00	
	<5	29	63	0.71	0.68	0.41, 1.14
	6–10	52	93	0.87	0.85	0.57, 1.27
	11–15	62	107	0.90	0.92	0.64, 1.33
	≤16	64	88	1.13	1.09	0.75, 1.59
					$p = 0.13$‡	

* Adjusted for age at diagnosis (5-year categories), study area (Hawaii, San Francisco, Los Angeles), ethnicity (Chinese, Japanese, Filipino), years since migration (≤1 year in West, 2–7 years in West, ≥8 years in West, born in West, ≥1 East-West move), education category (high school, some college, college), family history of breast cancer (first-degree, second-degree, none), and age at first full-term birth (≤19, 20–24, 25–29, >29 years, none). CI, confidence interval.

† p for trend.

‡ Excluding never use in trend calculations.

§ Excluding 31 cases and 26 controls with missing pregnancy information.

¶ Excluding OC use within 3 years of diagnosis (see Materials and Methods).

ation between duration of OC use and breast cancer risk among women who migrated ≥8 years ago, but not among recent migrants. Several studies have suggested that the increased risk of OCs is limited to young women. However, restricting the analyses to women under age 45 years or under age 40 years (data not shown) did not appreciably alter the results.

Ziegler et al. (3) previously reported that risk of breast cancer was 80 percent higher in women who had been in the United States for approximately a decade relative to more recent migrants. Additional adjustment for duration of OC use did not change this pattern. When women born in the West were used as the referent category, *after* adjustment for duration of OC use, women who had been in the United States ≥8 years were still at almost twice the risk of breast cancer (odds ratio (OR) = 0.67) as women who had been in the country 2–7 years (OR = 0.34).

DISCUSSION

Recent studies show that breast cancer risk increases rapidly when Asian migrants arrive in the United States (3, 4). In this study, we also found that OC use increased substantially with time since migration. However, OC use, analyzed from a variety of perspectives, was not associated with increased risk of breast cancer, and OC use could not explain the doubling in risk that occurred during the first decade after migration to the United States.

TABLE 4. Odds ratio (ORs) of breast cancer associated with duration of oral contraceptive (OC) use by ethnic group, study location, years since migration, and age at diagnosis,* in Asian-American women, 1983–1987

Effect modifier	Subgroup 1 (cases/controls)		Subgroup 2 (cases/controls)		Subgroup 3 (cases/controls)	
	OR*	95% CI	OR*	95% CI	OR*	95% CI
Ethnicity	Chinese (163/282)		Japanese (238/386)		Filipino (189/277)	
Never used OCs	1.00		1.00		1.00	
1–12 months use	1.69	0.82, 3.49	1.45	0.87, 2.43	0.81	0.43, 1.53
13–60 months use	1.17	0.63, 2.20	0.66	0.40, 1.08	1.00	0.50, 2.00
>60 months use	0.57	0.25, 1.33	0.83	0.46, 1.49	0.76	0.30, 1.93
Trend test	$p = 0.33$		$p = 0.11$		$p = 0.69$	
LR test†	$p = 0.73$					
Study Location	Hawaii (211/370)		Los Angeles (214/272)		San Francisco (165/303)	
Never used OCs	1.00		1.00		1.00	
1–12 months use	1.11	0.65, 1.90	1.19	0.65, 2.18	1.54	0.78, 3.07
13–60 months use	0.81	0.47, 1.37	0.69	0.35, 1.35	0.94	0.53, 1.67
>60 months use	0.75	0.39, 1.41	0.47	0.21, 1.02	0.83	0.37, 1.90
Trend test	$p = 0.23$		$p = 0.03$		$p = 0.53$	
LR test†	$p = 1.00$					
Years since migration	Born in West (252/355)		≥8 years (219/329)		2–7 years (51/140)	
Never used OCs	1.00		1.00		1.00	
1–12 months use	1.21	0.74, 1.98	1.02	0.57, 1.83	1.61	0.50, 5.15
13–60 months use	0.62	0.39, 0.98	0.88	0.50, 1.53	1.34	0.38, 4.66
>60 months use	0.83	0.50, 1.38	0.37	0.15, 0.92	1.55	0.13, 18.1
Trend test	$p = 0.12$		$p = 0.03$		$p = 0.78$	
LR test†	$p = 1.00$					
Age at diagnosis/reference age (years)	<45 (241/453)		≥45 (349/492)			
Never used OCs	1.00		1.00			
1–12 months use	1.09	0.66, 1.79	1.44	0.88, 2.34		
13–60 months use	1.00	0.62, 1.61	0.63	0.40, 1.01		
>60 months use	0.62	0.34, 1.14	0.82	0.45, 1.47		
Trend test	$p = 0.19$		$p = 0.09$			
LR test†	$p = 0.39$					

* Adjusted for age at diagnosis (5-year categories), study area (Hawaii, San Francisco, Los Angeles), ethnicity (Chinese, Japanese, Filipino), years since migration (≤1 year in West, 2–7 years in West, ≥8 years in West, born in West, ≥1 East-west move), education category (high school, some college, college), family history of breast cancer (first-degree, second-degree, none), and age at first full-term birth (≤19, 20-24, 25-29,>29 years, none). CI, confidence interval.

† LR test, likelihood ratio test for whether fit of mulitvariate logistic regression model is improved by fitting separate OC duration categories for each subgroup (compared with baseline model with duration of OC use for all subgroups combined).

‡ Excluding 35 controls and 18 cases who migrated ≤1 year prior to assigned reference age and 86 controls and 50 cases with more than one East-West move. This analysis was not adjusted for age at first full-term birth.

In the recently published Collaborative Study on Breast Cancer and Hormonal Contraceptives (23, 24), recent use of OCs was most strongly associated with breast cancer risk; 10 years after use ended, the risk returned to normal. We did not have information on OC use during the last 3 years prior to interview in this study (and therefore excluded OC use within 3 years of diagnosis). However, we found no increased risk associated with use 4–10 years prior to diagnosis, suggesting that if there is an effect of recent use in this group of Asian-American women, it must be of short duration.

A number of studies in non-Asian women (12–22, 31–34) have found an increased risk of breast cancer associated with OC use in young women, particularly associated with use at an early age. We did not find an effect of early use, but neither did two studies of Chinese women who lived in China (35, 36). A third study of Chinese women in Singapore found an odds ratio of 1.9 associated with use before first pregnancy, but this was based on 4 exposed cases and 4 exposed controls (37). The two studies conducted in China (35, 36) found a slightly increased risk associated with perimenopausal OC use.

Asian women who live in Asia have been shown (38–40) to have lower serum hormone levels than their White counterparts in the United States. The increase in

breast cancer risk that occurs during the first decade after migration could be due in part to a rise in serum hormones caused by life-style changes, and consequently increased breast cell proliferation (41). However, if this was true, then we hypothesize that recent migrants from the East who start taking OCs should experience a larger relative increase in circulating sex steroids than women born in the West, or women who migrated a decade ago (since the absolute OC dose used is the same). We would also hypothesize that recent migrants from the East who start taking OCs should experience a greater increase in breast cell proliferation rates than women born in the West (who, if similar to their White counterparts experience little or no increase in breast cell proliferation rates when they start using OCs (42–45)). Consequently, the association between OC use and breast cancer risk might be highest in these recent migrants, and lowest in women who were born in the West. The only odds ratios for breast cancer associated with OC use we observed above 1.0 were in fact among recent migrants. However, none of these odds ratios were statistically significantly different from 1.0. Women who migrated ≥8 years ago did not have elevated odds ratios for OC use, in fact, an apparent decrease in risk was observed with increasing duration of OC use. The three studies of Chinese women who lived in Asia failed to find an overall effect of OC use on breast cancer risk (35–37). A fourth study, the WHO Collaborative Study (46), suggested a modest (30 percent) increased risk associated with ever use in women who lived in China and the Philippines. None of these studies suggest that OCs increase the risk more in Asian women than in non-Asian women. On the other hand, these studies would be compatible with a hypothesis that Asian women metabolize estrogen differently, or that perhaps their breast tissue responds differently to rising estrogen levels than non-Asian women. In the future, we plan to study serum levels of a large number of endogenous hormones and growth factors, as well as urinary indicators of estrogen metabolism, in women from this study in order to further elucidate how hormones and growth factors relate to breast cancer development in Asian-American women.

In conclusion, this study suggests that oral contraceptive use can not explain the elevated risk observed in Asian women who migrated to the United States ≥7 years ago.

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